

4.8 CYPERMETHRINS (INCLUDING ALPHA- AND ZETA-CYPERMETHRIN) (118)

TOXICOLOGY

Cypermethrin is the ISO approved common name for (*RS*)- α -cyano-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate. Cypermethrin is a synthetic pyrethroid insecticide containing three chiral centres, giving a racemic mixture of eight isomers comprising four diastereoisomeric pairs. The cypermethrins are alpha-cyano- or type II pyrethroids. Cypermethrin was first evaluated by the 1979 JMPR, when a temporary ADI was established. New toxicological data were evaluated at the 1981 JMPR and an ADI of 0–0.05 mg/kg bw per day was established. Cypermethrin was reviewed by the present Meeting within the periodic review programme of the CCPR; this review included alpha-cypermethrin and zeta-cypermethrin, which had not previously been considered by the JMPR.

Cypermethrin and alpha-cypermethrin were considered by JECFA in 1996 and in 2002. In 2002, JECFA established a group ADI of 0–0.02 mg/kg bw, and recommended that JMPR should also consider this approach. The studies submitted to JECFA were available for consideration by the JMPR at its present meeting. Several studies on cypermethrin that were reviewed by JMPR in 1979 and 1981 were not available at the present meeting, but were considered in this evaluation on the basis of the JMPR summaries. The 2006 JMPR was made aware of a study of developmental neurotoxicity with zeta-cypermethrin that had not been submitted before the present meeting. This study was submitted during the meeting but was not evaluated in detail; however, based on a brief review, the Meeting concluded that this study was not critical for its final conclusion.

For alpha-cypermethrin, the specifications were established by the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS) and published as *WHO specifications and evaluations for public health pesticides: alpha-cypermethrin* (2006).⁴⁰

Most studies, excluding those described in previous JMPR monographs, were certified as having been performed in compliance with GLP and in accordance with the relevant OECD test guidelines.

Biochemical aspects

The fate of orally administered cypermethrin was studied in mice, rats, dogs, and humans, and alpha-cypermethrin was investigated in rats and humans. When administered orally to rats, cypermethrin and alpha-cypermethrin were partially absorbed, distributed widely in the tissues, and excreted rapidly. After a low single oral dose (2 mg/kg bw) of ¹⁴C-labelled cypermethrin or alpha-cypermethrin, approximately 50–75% of the radioactivity was excreted in the urine, with little in the expired air, and the remainder in the faeces. As most of the radiolabelled material in the faeces comprised the unmetabolized parent molecule, the role of biliary excretion appears to be minor, although this was not measured directly, and the amount in the urine represents approximately the amount absorbed. Maximum concentrations in the blood were reached at 3–4 hours after dosing at 2 mg/kg bw.

In rats given a single oral dose of ¹⁴C-labelled cypermethrin or alpha-cypermethrin at 2 mg/kg bw, the highest tissue concentrations of radioactivity were found in the fat (< 1% of the administered dose), followed by the skin. In rats and mice, radioactivity in the fat was identified as unchanged cypermethrin, present mainly as the *cis* isomer. Elimination of radiolabel from most tissues was rapid, but the elimination half-life of cypermethrin and alpha-cypermethrin in rodent adipose tissue and skin was prolonged (10–40 days). Repeat-dose studies in rats confirmed that cypermethrin accumulates in

⁴⁰ Available from http://www.who.int/whopes/quality/en/Alphacypermethrin_eval_april_2006.pdf

fat and skin, reaching a plateau after dosing for 4 weeks at 2 mg/kg bw per day. Concomitant increases in radioactivity also occurred in the plasma, liver and kidney, but concentrations were an order of magnitude lower than in fat.

In laboratory animals, cypermethrin was readily hydrolysed at the ester bond, followed by hydroxylation and conjugation of the cyclopropyl and phenoxybenzyl moieties of the molecule. Urinary metabolites consistent with a similar metabolic pathway in humans were recovered from orally dosed volunteers. The animal data indicated that there is little isomeric interconversion during metabolism of cypermethrin or alpha-cypermethrin.

Toxicological data

Cypermethrin has low to moderate acute oral toxicity in rats (LD₅₀, 163 to > 3000 mg/kg bw). This variability was only partly explicable by the vehicle used. The acute oral LD₅₀ of *cis*-cypermethrin in rats was 160–300 mg/kg bw, indicating that it is considerably more toxic than *trans*-cypermethrin, for which the LD₅₀ was > 2000 mg/kg bw under the same conditions. From these results, it would be predicted that alpha-cypermethrin is approximately twice as acutely toxic as cypermethrin. A wide range of acute oral LD₅₀ values in rats was also reported for alpha-cypermethrin (LD₅₀, 64 to > 5000 mg/kg bw). Similar studies with zeta-cypermethrin gave fairly consistent results (LD₅₀, 86–367 mg/kg bw). The dermal toxicity of cypermethrin and alpha-cypermethrin was low in rats (LD₅₀, > 1600 mg/kg bw and > 2000 mg/kg bw per day, respectively), as was the dermal toxicity of zeta-cypermethrin in rabbits (LD₅₀, > 2000 mg/kg bw), and inhalation toxicity was moderate for cypermethrin (LC₅₀, 1.260 mg/L) and alpha-cypermethrin (LC₅₀, 1.590 mg/L). Overall, the three isomeric mixtures displayed qualitatively similar profiles for acute toxicity in rats.

In rabbits, cypermethrin, alpha-cypermethrin and zeta-cypermethrin were slight eye irritants and slight skin irritants. Cypermethrin showed potential for skin sensitization in the maximization test in guinea-pigs, but was not a sensitizer according to the Buehler method, while alpha-cypermethrin was not a sensitizer in the maximization test, but zeta-cypermethrin was a skin sensitizer in the Buehler test. Cypermethrins also produce local paraesthesia (a tingling or burning sensation of the skin not associated with tissue damage) as an acute action that is distinct from irritancy.

Cypermethrin, alpha-cypermethrin and zeta-cypermethrin cause neurotoxicity in mammals and insects by causing a long-lasting prolongation of the normally transient increase in sodium permeability of nerve membrane channels during excitation. Salivation, and tremors that progress to clonic-tonic convulsions (choreoathetosis and salivation syndrome), along with gait abnormalities and ataxia are induced in rodents at high doses (> 100 mg/kg bw) but in dogs at lower doses (> 25 mg/kg bw), as seen in studies of acute toxicity and short-term studies of toxicity.

The main toxicological findings in repeat-dose studies in rodents were reduced weight gain, reduced food consumption, and at higher doses, signs of neurotoxicity (convulsions, tremors, hypersensitivity to touch and sound). Reduced weight gain and food consumption in rodents was observed with cypermethrin at dietary concentrations of 1000 ppm (equivalent to 50 mg/kg bw per day) and above. For alpha-cypermethrin these effects occurred at 100 ppm (equal to 11 mg/kg bw per day) in mice, while for zeta-cypermethrin the same effects were observed at 400 ppm (equal to 26 mg/kg bw per day) in rats. Dogs appeared to be the most sensitive species, with clinical signs of neurotoxicity being observed in the absence of body-weight loss at dietary concentrations of 600 ppm (equivalent to 15 mg/kg bw per day) and 120 ppm (equivalent to 3 mg/kg bw per day) for cypermethrin and alpha-cypermethrin respectively. Dogs dosed with alpha-cypermethrin for 3 months showed the usual clinical signs of pyrethroid toxicity, namely body tremors and variable incidences of head nodding, lip-licking, subduedness, ataxia, and agitation. The NOAEL for clinical signs in the 3-month study was 90 ppm (equivalent to 2.2 mg/kg bw per day). However, dogs dosed for 12 months showed no systemic toxicity. There was, however, abdominal skin reddening, skin reddening of the tail, including ulceration and necrosis of the tail in one male. The NOAEL for this effect was 60 ppm (equivalent to 1.5 mg/kg bw per day). There were no apparent methodological reasons for the disparity in clinical signs observed in the 3-month study in dogs, but not in the 12-month study in

dogs. Similarly, the local skin irritation effects, possibly secondary to paraesthesia, observed after 3 weeks at 120 ppm (equivalent to 3 mg/kg bw per day) in the 12-month study were not found at higher doses (270 ppm, equivalent to 6.7 mg/kg bw per day) in the 3-month study. It was not possible to discount the possibility that this may have been caused by accidental contact with food containing alpha-cypermethrin. For zeta-cypermethrin, there were no studies in dogs. However, repeat-dose studies of neurotoxicity involving functional observational battery tests in rats given diets containing zeta-cypermethrin indicated reduced landing footsplay and motor activity at 400 ppm (equal to 26 mg/kg bw per day).

There was no evidence of carcinogenicity with cypermethrin at dietary concentrations of up to 1600 ppm (equivalent to 240 mg/kg bw per day) in mice and at up to 1500 ppm (equivalent to 75 mg/kg bw per day) in rats. This was also the case in mice given diets containing alpha-cypermethrin at concentrations of up to 300 ppm (equal to 35 mg/kg bw per day), the highest dose tested.

Cypermethrin, alpha-cypermethrin and zeta-cypermethrin gave negative results in an adequate battery of studies of genotoxicity *in vitro* and *in vivo*.

In the absence of any carcinogenic potential in rodents and the lack of genotoxic potential *in vitro* and *in vivo*, the Meeting concluded that the cypermethrins are unlikely to pose a carcinogenic risk to humans.

In a three-generation study of reproductive toxicity in rats, adults receiving cypermethrin at a dietary concentration of 150 ppm (equal to 11 mg/kg bw per day) showed reduced body-weight gain and food consumption, and pups had lower body-weight gain during lactation at the higher dose of 750 ppm (equal to 56 mg/kg bw per day). Consistent with this, adult rats at 500 ppm (equivalent to 38 mg/kg bw per day) in a two-generation study of reproductive toxicity, also showed reduced body-weight gain and food consumption, but in this case litter size and litter weight were decreased at the same dose. In a two-generation study of reproductive toxicity with zeta-cypermethrin, decreased maternal body-weight gain and food consumption occurred at 375 ppm (equal to 22 mg/kg bw per day), along with decreased pup body weight. In contrast to the studies of reproductive toxicity with cypermethrin, clinical signs were observed in the dams and pups treated with zeta-cypermethrin at 22 mg/kg bw per day and above, although similar NOAELs were obtained (6 mg/kg bw per day). No effects on reproductive performance were observed with either cypermethrin or zeta-cypermethrin.

In studies of developmental toxicity with cypermethrin and alpha-cypermethrin in rats and rabbits, and with zeta-cypermethrin in rats, teratogenicity was not observed. The only developmental effect noted in any of these studies was a slight but statistically significant reduction in fetal weight in rats treated with alpha-cypermethrin when clinical signs of neurotoxicity, and decreased body-weight gain and food consumption were seen in the dams. The NOAEL for these effects was 9 mg/kg bw per day. There were no developmental effects in rabbits given alpha-cypermethrin at up to 30 mg/kg bw per day or cypermethrin at 700 mg/kg bw per day, the highest doses tested, but alpha-cypermethrin was relatively more maternally toxic than cypermethrin in rabbits, causing a decrease in body-weight gain at 30 mg/kg bw per day, while the dose of cypermethrin at which similar effects were seen was 700 mg/kg bw per day.

Studies of acute neurotoxicity in rats were performed with cypermethrin, alpha-cypermethrin and zeta-cypermethrin. With cypermethrin, reduced activity and gait abnormalities were observed at a dose of 20 mg/kg bw; the NOAEL was 4 mg/kg bw. At doses of 60 mg/kg bw and above, salivation, choreoathetosis, altered righting reflex, splayed limbs and flattened posture were observed; urination, landing foot splay and click response were increased; and arousal, grip strengths, touch response and tail-pinch response were decreased. Alpha-cypermethrin induced death, clinical signs, gait abnormalities, abnormal reactivity in the functional observational battery (FOB), and slight to very slight degeneration of sciatic nerve fibres at doses of 20 mg/kg bw and above, with males being more severely affected than females. The NOAEL was 4 mg/kg bw. With zeta-cypermethrin at a dose of 50 mg/kg bw, clinical signs were observed, with additional findings of FOB abnormalities and one female death at 250 mg/kg bw. The NOAEL was 10 mg/kg bw.

Overall, the limited database for zeta-cypermethrin indicated that its toxicity profile was similar to that for cypermethrin and alpha-cypermethrin.

The Meeting concluded that the existing database was adequate to characterize the potential hazard of cypermethrins to fetuses, infants and children.

Toxicological evaluation

The Meeting acknowledged that since racemic cypermethrin already includes a substantial proportion of alpha- and zeta-cypermethrin, and that all three cypermethrins are qualitatively similar in their toxicity and metabolism, an ADI established for alpha-cypermethrin could apply for all three substances. Since conventional testing of cypermethrin residues in treated commodities is unable to distinguish between the isomers, a group ADI is appropriate.

The Meeting established a group ADI of 0–0.02 mg/kg bw per day based on a NOAEL of 2.2 mg/kg bw per day for severe clinical signs of neurotoxicity in a 3-month dietary study in dogs treated with alpha-cypermethrin, and using a 100-fold safety factor. This NOAEL is supported by a similar NOAEL of 1.5 mg/kg bw per day for abdominal skin reddening and alopecia in a 12-month dietary study in dogs.

The Meeting established a group ARfD of 0.04 mg/kg bw based on the NOAEL of 4 mg/kg bw, and using a 100-fold safety factor. The NOAEL observed in a study of acute neurotoxicity was based on death, clinical signs, changes in FOB tests and degenerative changes to the sciatic nerve at higher doses. Although the database indicated that dogs were more sensitive than rats to neurotoxic effects, the delayed onset of clinical signs (2 days) after dosing at 6.75 mg/kg bw per day in the 3-month study in dogs suggests that the NOAEL in the study of acute toxicity in rats would also be adequate for the most sensitive species.

A toxicological monograph was prepared.

Levels relevant to risk assessment

(a) Cypermethrin

Species	Study	Effect	NOAEL	LOAEL
Mouse	2-year study of toxicity and carcinogenicity ^a	Toxicity	400 ppm, equivalent to 60 mg/kg bw per day	1600 ppm, equivalent to 240 mg/kg bw per day
		Carcinogenicity	1600 ppm, equivalent to 240 mg/kg bw per day ^d	—
Rat	3-month studies of toxicity ^{a, b}	Toxicity	400 ppm, equivalent to 40 mg/kg bw per day	1500 ppm, equal to 116 mg/kg bw per day
		Toxicity	150 ppm, equivalent to 7.5 mg/kg bw per day	1000 ppm, equivalent to 50 mg/kg bw per day
	Carcinogenicity	1500 ppm, equivalent to 75 mg/kg bw per day ^d	—	
		Parental toxicity	50 ppm, equal to 3.8 mg/kg bw per day	150 ppm, equal to 11 mg/kg bw per day
	Multigeneration reproductive toxicity ^{a, b}	Offspring toxicity	100 ppm, equivalent to 7.5 mg/kg bw per day	500 ppm, equivalent to 38 mg/kg bw per day
Developmental toxicity ^c	Maternal toxicity	17.5 mg/kg bw per day	35 mg/kg bw per day	
	Embryo/fetotoxicity	70 mg/kg bw per day ^d	—	

Species	Study	Effect	NOAEL	LOAEL
	Acute neurotoxicity ^c	Neurotoxicity	4 mg/kg bw	20 mg/kg bw
Rabbit	Developmental toxicity ^{b,c}	Maternal toxicity	450 mg/kg bw per day	700 mg/kg bw per day
		Embryo/fetotoxicity	700 mg/kg bw per day ^d	—
Dog	3-month studies of toxicity ^{a,b}	Toxicity	500 ppm, equivalent to 12.5 mg/kg bw per day	800 ppm, equal to 25 mg/kg bw per day
	1-year study of toxicity ^a	Toxicity	200 ppm, equal to 5.7 mg/kg bw per day	600 ppm, equal to 18 mg/kg bw per day
	2-year study of toxicity ^a	Toxicity	300 ppm, equivalent to 7.5 mg/kg bw per day	600 ppm, equivalent to 15 mg/kg bw per day

^a Dietary administration

^b Two or more studies combined

^c Gavage administration

^d Highest dose tested

(b) Alpha-Cypermethrin

Species	Study	Effect	NOAEL	LOAEL	
Mouse	3-month study of toxicity ^a	Toxicity	50 ppm, equal to 6.3 mg/kg bw per day	250 ppm, equal to 33 mg/kg bw per day	
		18-month study of toxicity and carcinogenicity ^a	Toxicity	30 ppm, equal to 3 mg/kg bw per day	100 ppm, equal to 10.6 mg/kg bw per day
			Carcinogenicity	300 ppm, equal to 35 mg/kg bw per day ^d	—
Rat	3-month study of toxicity ^a	Toxicity	180 ppm, equivalent to 18 mg/kg bw per day	540 ppm, equivalent to 54 mg/kg bw per day	
	Developmental toxicity ^c	Maternal toxicity	9 mg/kg bw per day	18 mg/kg bw per day	
		Embryo/fetotoxicity	9 mg/kg bw per day	18 mg/kg bw per day	
	Acute neurotoxicity ^c	Neurotoxicity	4 mg/kg bw	20 mg/kg bw	
Rabbit	Developmental toxicity ^c	Maternal toxicity	15 mg/kg bw per day	30 mg/kg bw per day	
		Embryo/fetotoxicity	30 mg/kg bw per day ^d	—	
Dog	3-month study of toxicity ^a	Toxicity	90 ppm, equivalent to 2.2 mg/kg bw per day	270 ppm, equivalent to 6.7 mg/kg bw per day	
	1-year study of toxicity ^a	Toxicity	60 ppm, equivalent to 1.5 mg/kg bw per day	120 ppm, equivalent to 3 mg/kg bw per day	

^a Dietary administration

^b Two or more studies combined

^c Gavage administration

^d Highest dose tested

(c) Zeta-cypermethrin

Species	Study	Effect	NOAEL	LOAEL
Rat	3-month study of toxicity ^a	Toxicity	250 ppm, equal to 17 mg/kg bw per day	500 ppm, equal to 34 mg/kg bw per day
	Multigeneration reproductive toxicity ^a	Parental and offspring toxicity	100 ppm, equal to 6 mg/kg bw per day	375 ppm, equal to 22 mg/kg bw per day
	Developmental toxicity ^c	Maternal toxicity	12.5 mg/kg bw per day	25 mg/kg bw per day
		Embryo/fetotoxicity	35 mg/kg bw per day ^d	—
	Acute neurotoxicity ^c	Neurotoxicity	10 mg/kg bw	50 mg/kg bw
	3-month study of neurotoxicity ^a	Neurotoxicity	75 ppm, equal to 5 mg/kg bw per day	400 ppm, equal to 26 mg/kg bw per day

^a Dietary administration

^b Two or more studies combined

^c Gavage administration

^d Highest dose tested

Estimate of acceptable daily intake for humans

0–0.02 mg/kg bw

Estimate of acute reference dose

0.04 mg/kg bw

Information that would be useful for continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposures

Critical end-points relevant for setting guidance values for exposure to cypermethrins*Absorption, distribution, excretion and metabolism in mammals*

Rate and extent of oral absorption	T _{max} ~3 h; approximately 50–70% absorbed
Dermal absorption	Approximately 1% in humans
Distribution	Throughout the body; highest levels in fat, present mainly as <i>cis</i> -isomers
Potential for accumulation	The elimination half-life in fat was 10–25 days after a single oral dose; radioactivity accumulated in fat and skin after repeated oral dosing
Rate and extent of excretion	Rapid; > 95% excreted in 48 h
Metabolism in animals	Extensive, no unchanged cypermethrin excreted in the urine
Toxicologically significant compounds	Parent

<i>Acute toxicity (cypermethrin)</i>			
Rat, LD ₅₀ , oral		200 to > 3000 mg/kg bw	
Rat, LD ₅₀ , dermal		> 1600 mg/kg bw (xylene vehicle); > 4800 mg/kg bw undiluted	
Rat, LC ₅₀ , inhalation		1.260 mg/L air	
Guinea-pigs, skin sensitization (test method used)		Sensitizer (maximization); non-sensitizer (Buehler)	
<i>Acute toxicity (alpha-cypermethrin)</i>			
Rat, LD ₅₀ , oral		64 to > 5000 mg/kg bw, depending on vehicle	
Rat, LC ₅₀ , inhalation		1.590 mg/L air	
<i>Acute toxicity (zeta-cypermethrin)</i>			
Rat, LD ₅₀ , oral		86–367 mg/kg bw (corn oil vehicle)	
<i>Short-term studies of toxicity</i>			
Target/critical effect		Clinical signs of neurotoxicity	
Lowest relevant oral NOAEL		2.2 mg/kg bw per day (90-day study in dogs)	
Lowest relevant dermal NOAEL		20 mg/kg bw per day (21-day study in rabbits)	
Lowest relevant inhalation NOAEL		0.050 mg/L (21-day study in rats)	
<i>Genotoxicity</i>			
		No genotoxic potential	
<i>Long-term studies of toxicity and carcinogenicity</i>			
Target/critical effect		Reduced body-weight gain and food consumption	
Lowest relevant NOAEL		7.5 mg/kg bw per day (2-year dietary study in rats)	
Carcinogenicity		Not carcinogenic in rats and mice	
<i>Reproductive toxicity</i>			
Reproduction target/critical effect		No reproductive effects; decreased pup body weight	
Lowest relevant reproductive NOAEL		6 mg/kg bw per day (rats)	
Developmental target/critical effect		Decreased fetal weights (rats)	
Lowest relevant developmental NOAEL		9 mg/kg bw per day	
<i>Neurotoxicity</i>			
Target/critical effect		Clinical signs, changes in FOB tests and degenerative changes to the sciatic nerve	
Lowest relevant NOAEL		4 mg/kg bw per day (single-dose study in rats)	
<i>Delayed neurotoxicity</i>			
Target/critical effect		No delayed effect	
Lowest relevant NOAEL		> 1000 mg/kg bw per day (hens)	
<i>Medical data</i>			
		Paraesthesia after dermal exposure	
Summary for cypermethrins, including alpha-cypermethrin and zeta-cypermethrin			
	Value	Study	Safety factor
Group ADI	0–0.02 mg/kg bw per day	Dog, 3-month dietary study with alpha-cypermethrin	100
Group ARfD	0.04 mg/kg bw	Rat, study of acute neurotoxicity with alpha-cypermethrin	100